Paediatric Type 2 Diabetes – escalation of medical treatment

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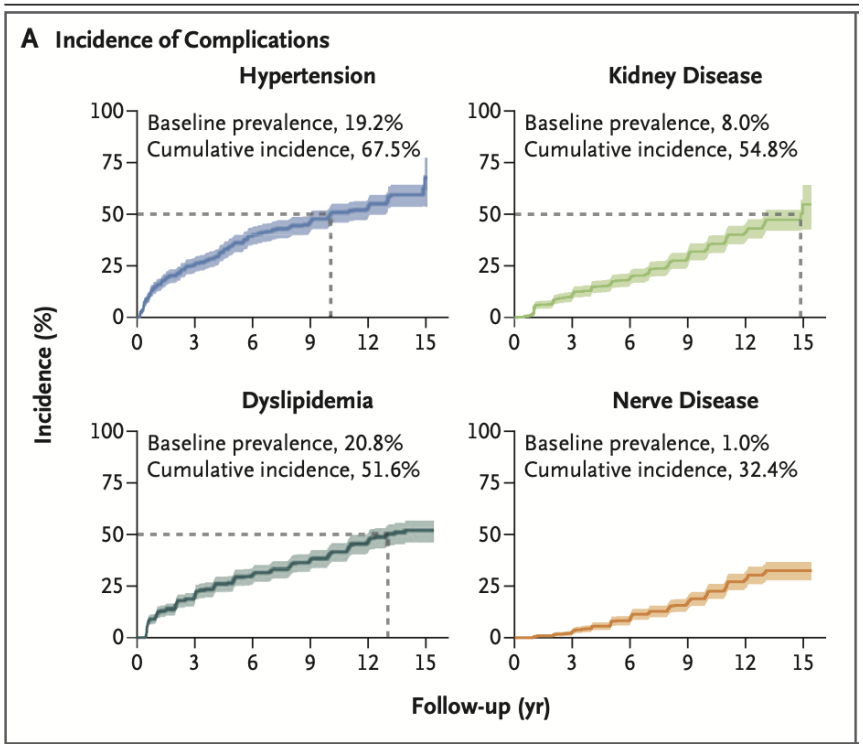
Helping all children and young people with diabetes in East London to lead a healthy, happy life.

Barts and The London
School of Medicine and Dentistry

Outline

- Outcomes of T2D in young people
- Aims of treatment in T2D, NICE guidance
- Medical treatment at diagnosis
- Medical treatment after diagnosis
- Funding of new drugs

Long term complications in T2D in TODAY study



- Follow up of 500 CYP with T2D
- Previously in TODAY study (2004-2011)
- Age 26.4±2.8 years
- Mean time since diagnosis 13.3±1.8 yrs

- Conclusion: Complications increase with increased duration of T2D

Today Study Group, NEJM 2022

Aims in T2D management (ACDC/NICE)

- HbA1c: < 48 mmol/mol
- Glucose: Preprandial 3-7 (3.9-7 if on insulin), postprandial 4-9 mmol/L (NICE)
- Weight loss: 5-10% in 3-12 months and long term BMI < 85TH centile:
- Co-morbidity screening and treatment

Important: escalate treatment if HbA1c not < 48

Recommendations (ACDC/NICE)

- HbA1c should be measured every 3 months in CYP with T2DM
- HbA1c targets should be individualised, noting the low risk of hypoglycaemia.
- **Intensify treatment if HbA1c is not below 48mmol/mol (6.5%) at 3 months or if BG frequently > 7 mmol/L premeal or > 9 mmol/L 2 hrs postmeal.**
- Individualise HbA1c Target after the first 3 months but aiming to keep below 48mmol/mol (6.5%)

Medical treatment at diagnosis (NICE)

- If BG > 33, consider Hyperglycaemic hyperosmolar state (HHS)
- If ketosis is present or HbA1c > 8.5% → start insulin treatment (NICE)
- Metformin 500 mg OD to increase to 2000 mg daily (regular, liquid or slow release)
- If BG > 14, give correction with Novorapid, or start long-acting insulin (eg 0.2 U/kg)
- If HbA1c > 8.5%, consider insulin unless BG mostly < 14 (RLH)

Glucose and ketone testing

- ADA/ISPAD/NICE/ACDC: BG should be monitored in all patients with T2
- Frequency should be tailored to the individual based on treatment-factors.
- **RLH:**
- **If on MDI**: BG at least 5 times a day to adjust doses, give corrections and monitor for hypoglycaemia, similar to T1D
- **If stable, and not on MDI**:
  - When BG still often > 9 → test fasting BG and 2 hrs after each meal, and pre-meals if needed
  - When BG mostly < 9 → test once a week fasting BG and once a day post-meal
- **CGM/Flash**: if insulin dependent, or learning disability, severe/frequent hypoglycaemia, or BG testing > 8 x per day (**NICE, 2023**).
- **Ketone meter**: test ketones if BG > 14

CGM (NICE 2023)

Eligible for CGM in T2D:

- Anyone on **insulin treatment** OR
- Have a **need, condition or disability that means they cannot engage in capillary BG monitoring** OR
- Would otherwise be advised to **monitor at least 8 times per day**

Choose the appropriate device of CGM with the CYP suiting their needs

Choose the cheapest if more than one fits their needs

Clinics, commissioners should monitor who is using CGM and identify groups with a lower uptake, and make plans to engage with those groups.

NICE guideline T1/T2D in CYP, Fou L, Gevers BMJ 2023

Hypoglycaemia

- Hypoglycaemia treatment
  - if on insulin → BG <3.9 needs treating in same way as T1D
  - if not on insulin → only BG <3.0 needs treating (hypoglycaemia not expected)

Medical management after initial diagnosis

See at the latest 4 weeks after diagnosis/start of Metformin

- Ensure taking Metformin 2000 mg per day (**Liquid or SR Metformin** if needed)
- **Wean insulin as much as possible**

At 3 months:

- If no further possibility to reduce insulin doses, or Metformin monotherapy not sufficient to reach target of hbA1c < 48 or frequent BG outside normal range, **start GLP1RA, eg Liraglutide (**0.6 mg SC OD to max dose of 1.8 mg) and wean insulin when possible (10-25% at a time)

Referral (age 11.5 yrs)

- 11.5 yr referred from gastro enterologist, fatty liver, concerns about obesity
- Height 153.6 cm, weight 104 kg, BMI 44.1 kg/m2. BP 98th centile.

- OGTT performed: BG 5 -- > **15.5 mmol/L**. **HbA1c 52**. Anti GAD, IA2, ZnTF8 negative.
- **Diagnosis of T2D**
- C peptide 416, **ALT 62**, cholesterol 4.2 mmol/L, LDL 2.3 mmol/L, urine alb/creat 0.3
- Sleep study: mild OSA.

- Started Metformin 500 mg OD → BD → 1000 mg BD
- 1 month later: **HbA1c 45**, lost 1 kg.

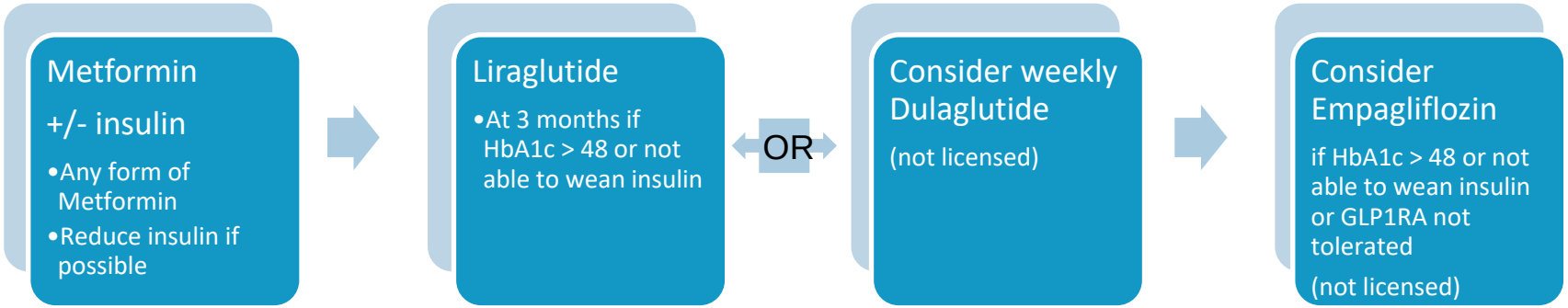
Progress (age 11-12 yrs)

- 1 month later: **HbA1c 51**, weight 105 kg (+ 2 kg), random BG 9.6.
- Not on full dose Metformin. Advised BG testing and full dose Metformin.
- Referred to CAHMS.
- Dietitian: attempted phone call

- 3 months later: phone review due to **pandemic**. Not testing BGs regularly
- Advised to take Metformin together with his mum and to do post meal BGs

- 3 months later (Oct 2020): hardly testing BGs
- Weight **– 8kg (98kg)** , **HbA1c 130**, **BG 16**, ketones neg. **ALT 241**
- **Start Novorapid corrections if BG > 14 with ISF 1:2, and admit**

Algorithm for drug treatment in CYP with T2D (NICE)



0.6→1.2→1.8 mg *
sc OD
(weekly increments)

0.75-1.5 mg *
sc once weekly,
Increase to 3.0 mg
(max dose 4.5 mg)

10 mg OD PO *,
If at 3 months Hba1c>48
Increase to 25 mg

* if > 10 yrs and
use lowest possible dose

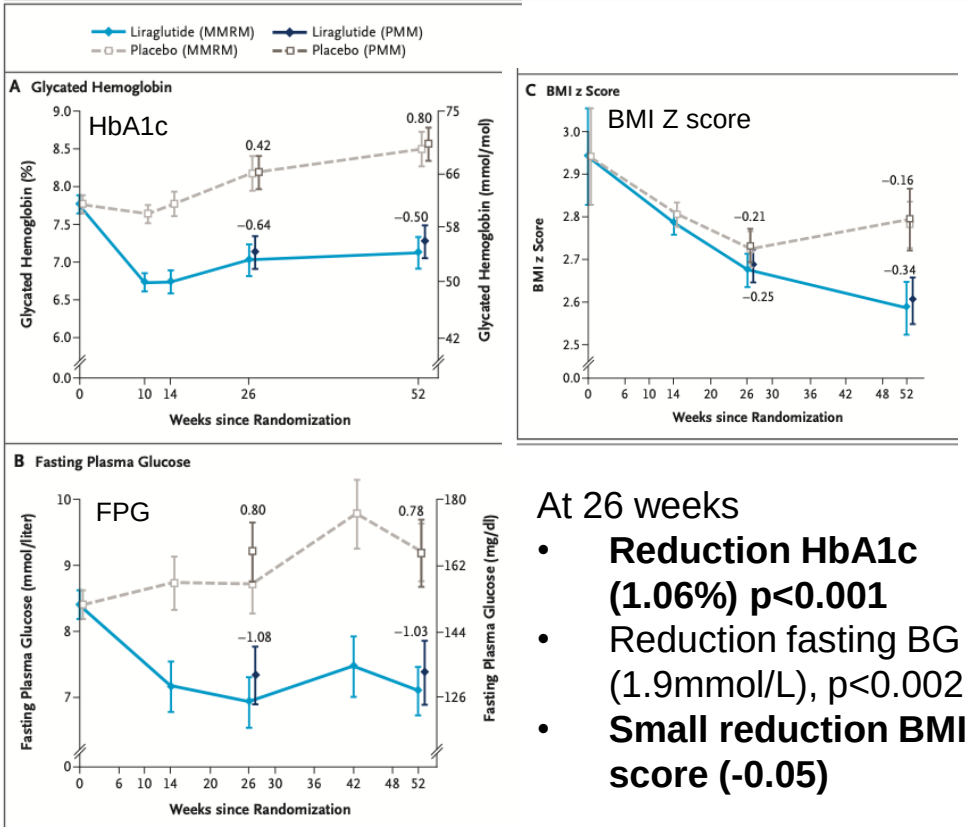
NICE guideline T1/T2D in CYP, Fou L, Gevers BMJ 2023

Liraglutide (Victoza)

- Glucagon-like peptide 1 receptor agonist (GLP1-R agonist)
- Increases insulin secretion, suppresses glucagon secretion and slows gastric emptying
- **Licence**: T2D if existing treatment fails to achieve good glycaemic control in CYP from 10 yrs of age with BMI > 85th centile
- **Now recommended by NICE (2023) for paediatric T2 diabetes**

- Can be used as monotherapy, or with Metformin and/or insulin, or SGTL2 inhibitors
- Once daily sc injections.
- Start 0.6 mg, increase weekly or more slowly to 1.2 mg and max 1.8 mg OD
- Contra-indications: gastroparesis, IBD, pregnancy, previous pancreatitis (FH of MEN?)
- Drug interaction: lisinopril, not with OCP

Liraglutide vs placebo for 26 weeks, OLE to 52 weeks



Tamborlane, NEJM 2019

At 26 weeks

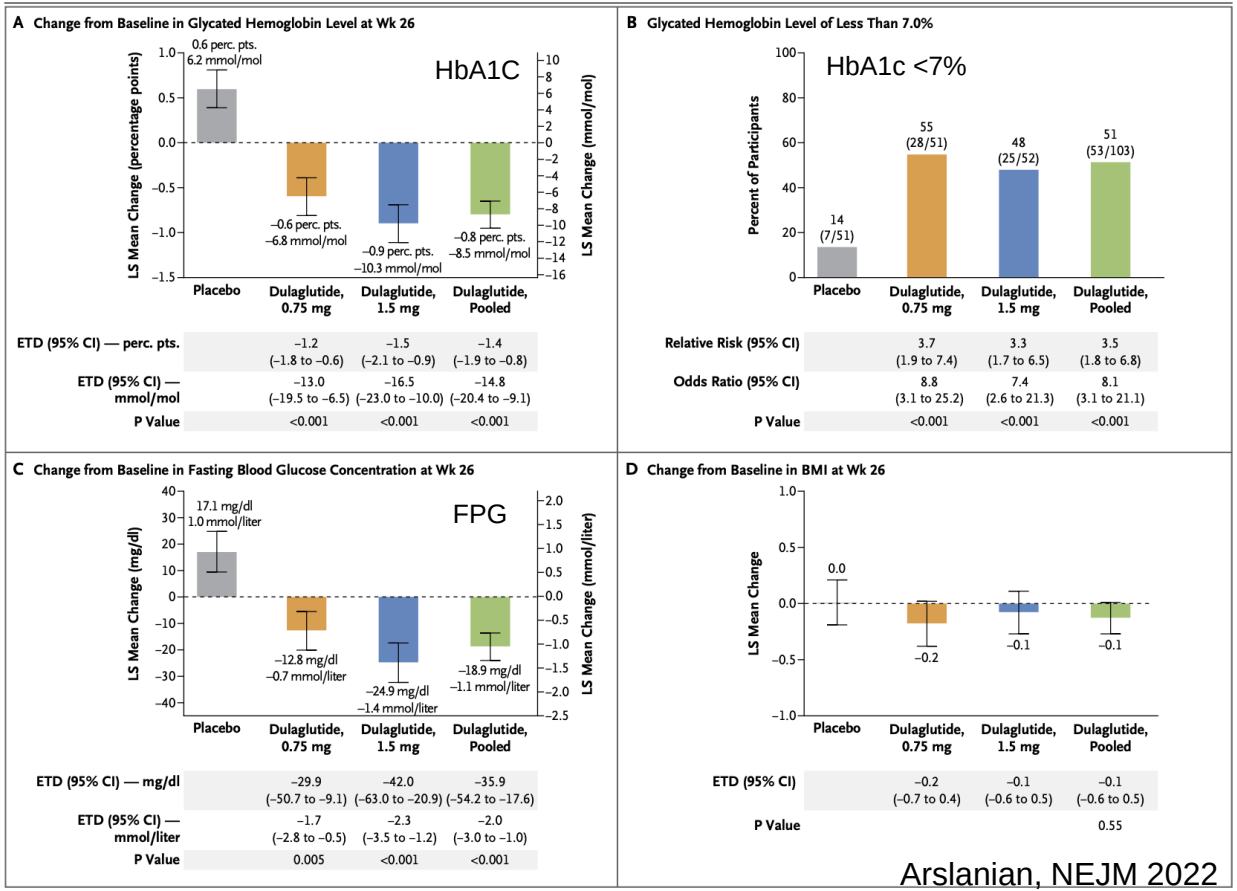
- **Reduction HbA1c (1.06%) p<0.001**
- Reduction fasting BG (1.9mmol/L), p<0.002
- **Small reduction BMI Z score (-0.05)**

- 10-17 yrs old, T2D
- BMI > 85th centile
- HbA1c 6.5-11% if on Metformin or insulin, or 7-11%

Side Effects Liraglutide vs placebo

- **Gastro-intestinal** (nausea, diarrhea, vomiting, abdominal pain) – 20-25%
- **55% of patients at max dose in 3 weeks** (not all patients required max dose)
- **Hypoglycaemia** 45% vs 25%, none severe
- **Lipase higher** in Liraglutide vs placebo (but in normal range)
- **DKA** (if insulin weaned to quickly), **pancreatitis and thyroid disorder** (BNF)
- Warn for signs of DKA and pancreatitis.

Dulaglutide 1.5 mg/ 0.75 mg/ placebo **once weekly** 26 weeks



Arslanian, NEJM 2022

Results vs placebo:

- **HbA1c**: - 0.8% vs +0.6% (p<0.001)
- **HbA1c < 7.0%:** 51% vs 14% (p<0.001)
- **Fasting glucose**: -1.1 mmol/L vs +1.0 mmol/L (P<0.001)
- **BMI**: -0.1 kg/m^2 vs 0.0 (non significant)
- **1.5 mg most effective**

Other GLP, GIP, glucacon receptor agonists

- **Exenatide (Byetta)** for **T2D** in CYP (**from 10 yrs**), **once weekly SC injection**
  - o HbA1c decreased vs placebo (-0.36 vs +0.49%), no effect on BMI
- **Liraglutide (Saxenda)** for **obesity** (**from 12 yrs**), **OD SC, max 3.0 mg**
  - o **BMI reduction -4.7**% after 26 weeks, 44% vs 19% reduced BMI by >5%, weight loss -5.0%
- **Semaglutide (Wegovy),** for **obesity (+/- T2D, from 12 yrs**), **once weekly SC 2.4 mg** (STEP-TEENS)
- o **BMI reduction 16% vs +0.6%** after 68 wks, weight loss 15%, HbA1c -0.4% vs 0.1%**,** 4% had T2D

Adults: Semaglutide (Wegovy), for **T2D and obesity > 18 yrs**, **once weekly SC injection**

- o Weight loss 15-17%
- **Adults: Semaglutide (Rybelsus), daily oral :** for T2D, HbA1c reduction 1.5%, weight reduction 5%
- **Adults: Orforglipron (non peptide) daily oral**: for obesity: 12.5 % weight reduction
- **Adults: Tirzepatide** (double GLP1, GIP agonist): for obesity
- **Adults**: **LY3437943**, triple GIP, GLP-1, and glucagon receptor agonist: for T2D: HbA1c -1.4% (Phase 1B)

Kelly, NEJM 2020, Arslanian, NEJM 2022, Shankar Ped Diab 2022, Tamborlane, Diab Care 2022, Weghuber, NEJM 2022

Admission with HbA1c > 130 (age 12.5 yrs)

- **Admitted** to assess BG profile, corrections if BG > 14 (required 3 x 2U NR overnight)
- **Start Liraglutide sc OD 0.6 mg**
- **Added Tresiba 8 U**
- **Strengthened Novorapid corrections to ISF 1:1**
- **Switched to slow release Metformin 2000 mg OD**

- Psychologist re-introduced.
- **Start Freestyle Libre**
- **Increased Liraglutide to 1.8 mg** OD sc over next few weeks

Progress (age 13-14 yrs)

- Nov 2020: mother passed away. Dad stopped working. Aunt from India came over.

- Jan 2021: HbA1c 60 (from >130)
- March 2021: HbA1c 68, weight 104 kg
- June 2021: HbA1c 85, weight 107 kg
- Oct 2021: Hba1c **116**, weight 105 kg, **ALT 91**, **Tresiba increased, refused admission**
- Dec 2021: Hba1c 108, weight 102 kg
- March 2022: HbA1c 102, weight 108 kg, **ALT 178**, not scanning FS Libre, aim to admit, weekly updates
- **May 2022: HbA1c 108, weight 110-120 kg, ALT 202, admission for optimisation**.

Admission (age 14 yrs)

- HbA1c 108
- **Changed to Saxenda** (Liraglutide to 2.4 mg and then 3.0 mg OD)

Also:

- Changed to Metformin SR again.
- Increased Tresiba dose
- Started Dexcom.
- Repeated dietary and exercise advise

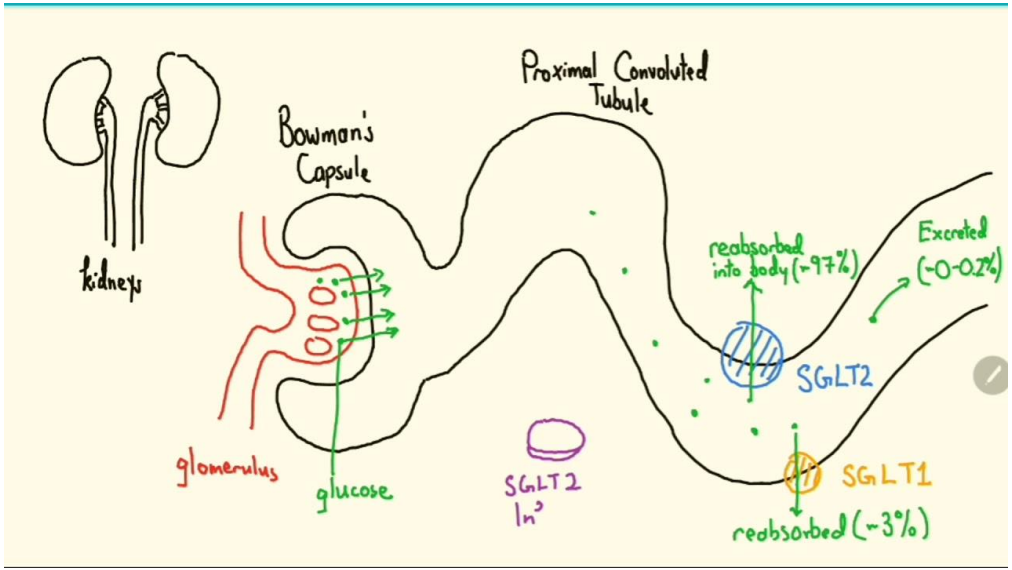
Result: weight stable, HbA1c improved to 99 mmol/mol (from 108)

Progress (age 14-15 yrs)

- June 2022: **HbA1c 89 mmol/mol** (from 108), **weight 108 kg**, **increase Saxenda to 3.0 mg**
- Repeat pancreas antibodies: negative. DNA for obesity gene panel – not performed.
- Oct 2022: **HbA1c 69 mmol/mol, weight 116 kg**, **agreed to gym.**
- Dec 2022: HbA1c 79 mmol/mol, weight 113 kg, **agreed to meal replacement shake OD**
- Jan 2023: hbA1c 89 mmol/mol , weight 113 kg, **BP 140/87 mmHg**, **not started MR, start lisinopril 5 mg od, Tresiba increased, agreed to gym, continuing psych input.**
- March 2023: HbA1c 87 mmol/mol , weight 111 kg, BP 123/84, **tried but stopped meal replacement drinks, going to gym twice a week, agreed to referral for bariatric surgery for information only, lisinopril not started, increased Tresiba.**
- April 2023: **HbA1c 99**, weight 111 kg, **BP 134/86. No MR shakes, not going to gym, refused lisinopril → admission for optimisation**

SGLT2 inhibitors

- inhibit SGLT2 (Na/glucose co transporter) in proximal renal tubule
- Increase urinary glucose concentration and thus lower blood glucose
- Oral tablets
- Extremely effective in adults with T2D, and have additional positive cardiovascular effects



SGLT2 inhibitors in T2 in CYP

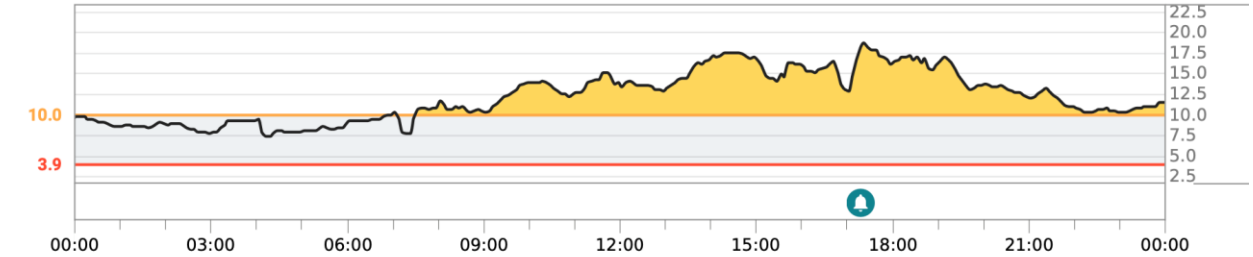
- **SGLT2 inhibitors: inhibit SGLT2 (Na/glucose transporter) in proximal renal tubule, once daily tablets**
- - **Dapagliflozin** (10-24 yrs): (Astra Zeneca) (licensed, no NICE approval)
    - o **no effect on HbA1C** in intention-to-treat analysis
    - o subanalysis of compliant patients Hba1c -0.51 vs +0.62%
  - **Empagliflozin**/Linagliptin: **HbA1c -0.84% vs placebo** Linagliptin no effect (Boerhinger, DINAMO)
  - **Dapagliflozin**/Saxagliptin : **Dapa HbA1c -1.0% vs placebo** Saxa no effect (Astra Zeneca T2NOW)
  - Ertugliflozin: no data available yet (Merck VERTIS study)

- **Side effects SGLT2 inhibitors:** DKA (in Type 1 diabetes), genital infections/gangrene, hypoglycaemia
- **Warning MHRA/BNF: stop when DKA suspected or when hospitalized with severe illness/trauma.**

Tamborlane, Lancet Diab Endocr 2022
Tahrani, Nat Rev Endo 2016; Laffel, Lancet Diab Endocr 2023

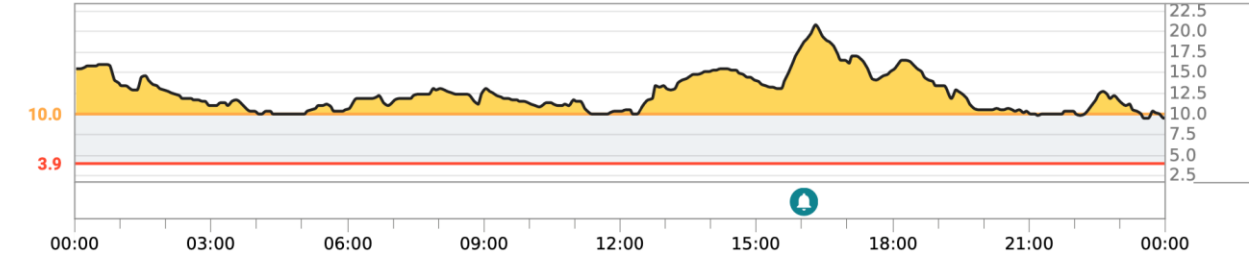
Before SGLT2 inhibitor (in hospital)

Thu, 20 Apr 2023

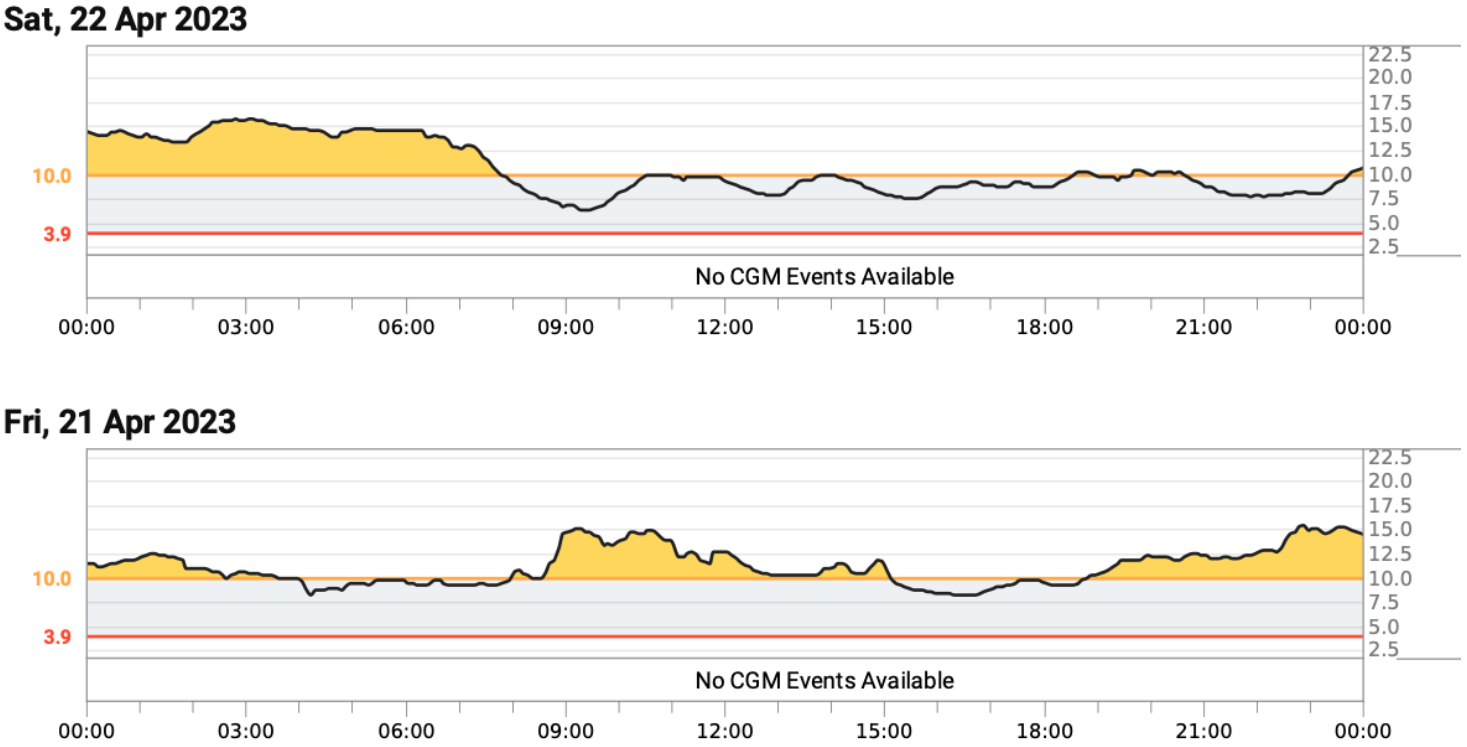


Time	Event	Details	Glucos
17:17	Alert	High	18.1 m

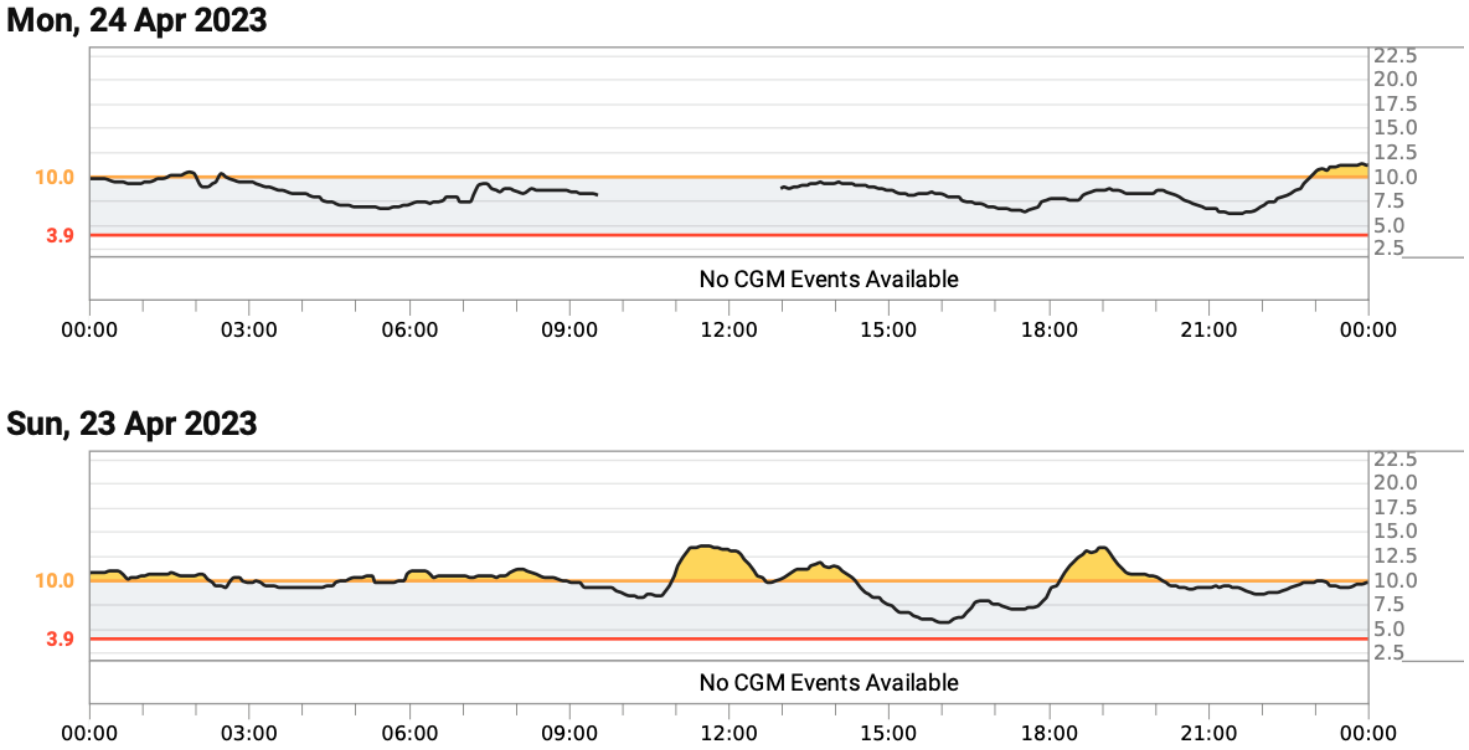
Wed, 19 Apr 2023



Empagliflozin 10 mg from 21 April 2023



Empagliflozin 10 mg from 21 April 2023



Progression (age 15 yrs)

June 2023: HbA1c improved from **99 to 82**, RBG 8.9

- Dexcom: 49% in range, no hypoglycaemia
- Weight 110.9 k (-0.3 kg)
- ALT improved to 79

October 2023: **HbA1c 83**, ALT 107

DPP4 inhibitors have no role in T2D treatment

Di-peptidyl peptidase inhibitors (oral) → reduce degradation of GLP1

- **Sitagliptin** (Januvia/Janumet Merck)
  - no effect on HbA1c
- **Saxagliptin** (Onglyza, Astra Zeneca) :
  - no data available from Saxagliptin only study
  - T2NOW study: Saxagliptin with/without dapagliflozin – Saxagliptin no significant effect (-0.44%)
- **Linagliptin**: 1mg/5mg/placebo, 12 wks
  - 0.38% and 0.48% reduction in HbA1c (not significant)

Shankar Ped Diab 2022, Jalaludin Paed Diab 2022
Tamborlane, Ped Diab 2017

Questions at panel discussion

Barts Health Paediatric Diabetes Team

Type 2 focus group
Evelien Gevers, consultant
Nicky Moore, Band 8 PDSN
Waseema Skogen, dietitian
Elizabeth Nash, psychologist
Nish Patel, database manager
Yasmin Khatun, database admin
Maggie Murphy, secretary

Current consultants RLH
Evelien Gevers (Lead T2)
Ruben Willemsen (Lead T1)
Claire Hughes
Pratik Shah
Rathi Prasad

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